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Fidaxomicin for the Treatment of *Clostridium difficile*-Associated Diarrhea (CDAD)

FDA Briefing Document for
Anti-Infective Drugs Advisory Committee Meeting
April 5, 2011

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I. BACKGROUND

Optimer Pharmaceuticals, Inc. submitted New Drug Application NDA 201,699 for Dificid™ (fidaxomicin tablets) on November 29, 2010. Fidaxomicin is a macrolide antibacterial with an 18-membered ring that is microbiologically active against *Clostridium difficile*. It has a narrow spectrum antibacterial profile and has bactericidal activity against *Clostridium difficile*. In addition, it is poorly absorbed and exerts its activity in the gastrointestinal (GI) tract. The Applicant's proposed indication for fidaxomicin is the treatment of adults with *Clostridium difficile* infection (CDI), also known as *Clostridium difficile*-associated diarrhea (CDAD), and prevention of recurrences.

The drug product is supplied as 200-mg tablets. The proposed dose regimen for fidaxomicin is 200 mg twice daily for 10 days.

This briefing document summarizes the information submitted in the fidaxomicin NDA. The last section of this document (**VII**) highlights the expected issues for discussion at the advisory committee meeting.

II. CLINICAL DEVELOPMENT

Fidaxomicin has been administered to 580 patients at the proposed to-be-marketed dose. Two Phase 3 trials assessed the safety and efficacy of fidaxomicin in the treatment of CDAD. In addition, an open-label phase 2A dose ranging trial was conducted in patients with CDAD that assessed 3 doses of fidaxomicin (100 mg/day, 200 mg/day, and 400 mg day) with sixteen patients randomized to each dose group.

Description of the Phase 3 trials is given below in Table 2.1

Table 2.1: Overview of the Phase 3 Trials

Trial	Description	Treatment Regimens	#Patients Randomized	#Patients Treated
101-1-C-003	Randomized, double-blind, multicenter, comparator-controlled study in CDAD patients. Study Centers: 102 sites (23 Canada and 79 US) Conducted: 5/2006 – 8/2008	Fidaxomicin 200 mg q12h for 10 days	302	300
		Vancomycin 125 mg q6h for 10 days	327	323
101-1-C-004	Randomized, double-blind, multicenter, comparator-controlled study in CDAD patients Study Centers: 96 (11 Canada, 30 US, and 45 Europe) Conducted: 4/2007 – 12/2009	Fidaxomicin 200 mg q12h for 10 days	265	264
		Vancomycin 125 mg q6h for 10 days	270	260

The applicant conducted two clinical trials, 101-1-C-003 and 101-1-C-004, that we refer to as trial 003 and trial 004, respectively.

The two trials used identical protocols, although the total sample size and the number and location of investigative sites varied. Both trials used multi-national, multi-center, double-blind, randomized (1:1), parallel group designs. Both trials compared fidaxomicin 200 mg PO q12h with vancomycin 125 mg PO q6h in patients with *Clostridium difficile*-associated diarrhea. The dosing duration for both treatments was ten days in both trials. An End-of-Therapy (EOT) visit was conducted on Day 10-11 and clinical response (the primary outcome) was assessed. Weekly contacts with subjects were made thereafter (Day 17 ±1 day, Day 24 ±1 day, Day 31 ±1 day) until recurrence or Post-study Visit [Days 36-40 (or at least 25 days after last dose of study medication)].

The randomization was stratified by prior CDAD episode with two strata: (1) no prior CDAD episode in the last 3 months or (2) a single prior CDAD episode in the last 3 months.

1. Endpoints:

The primary efficacy endpoint is clinical cure as assessed by the Investigator at the EOT visit. Clinical responses (cure/failure, recurrence) were based on the Investigator's assessment of subjects' clinical parameters, most importantly based on their diarrhea status.

In addition, other efficacy endpoints examined were recurrence assessed at least 25 days after cure and the last dose of study medication, as well as global cure (defined as achieving cure and not having a recurrence at any time up to the Post-study Visit), and Time-to-Resolution of Diarrhea (defined as the time from start of treatment to achieving resolution of diarrhea sustained through EOT).

Definition of Clinical response at the test-of-cure (TOC) assessment (10 days after starting treatment, i.e. EOT $\pm$ 2 days):

Clinical Cure:

- Subjects who, in the opinion of the Investigator, require no further CDAD therapy 2 days after completion of study medication will be considered cured.
- Subjects who have 3 or fewer unformed stools for 2 consecutive days and remain well prior to the time of study medication discontinuation will be considered cured.
- Subjects who at EOT have had a marked reduction in the number of unformed stools and who have residual and mild abdominal discomfort interpreted as recovering bowel by the Investigator may be tentatively considered cured at that time providing no new anti-infective CDAD therapy has been initiated. Subjects who are considered cured based on stabilization and improvement in CDAD signs and symptoms will be evaluated 2-3 days after the end of study medication. In the

event that their signs or symptoms of CDAD worsen, they will be designated primary failures.
- Subjects who enter the study without signs or symptoms of CDAD, other than diarrhea, will be evaluated as failures on the basis of continued diarrhea alone as defined in this protocol.
- Subjects having a rectal collection device who are passing liquid stools periodically during the day will be considered to have resolution of diarrhea when the volume (over a 24 hour period) is decreased by 75% compared to admission or the subject is no longer passing liquid stools.

Clinical Failure:

- Subjects who, in the opinion of the Investigator, require additional CDAD therapy will be considered a failure.

The Investigator was to base his/her clinical impression on the need for additional CDAD therapy on the subject's CDAD status, inclusive of the presence of diarrhea and other signs/symptoms of CDAD including: fever >38.0°C, elevated WBC >13,000/mL, or abdominal pain of moderate severity or greater lasting one hour or more and/or abdominal tenderness of at least moderate severity, including any peritoneal signs.

Definition of Recurrence:

Subjects who remain in the study up to the Post-study visit (Study Day 36-40) or who recur prior to that will be evaluated for recurrence and non-recurrence using the following definitions:

Recurrence is the re-establishment of diarrhea to an extent (frequency of passed unformed stools) that is greater than that noted on the last day of study medication with the demonstration of either toxin A or B or both of *C. difficile* and, in the Investigator's opinion, require retreatment with CDAD anti-infective therapy. Subjects designated as evaluable for recurrence must have positive toxin demonstrated in the stool. If a rapid screening test is used which fails to demonstrate toxin, then a confirmatory test using a non-rapid method must be used.

Non-recurrence is the maintenance of a non-diarrheal state up to and through the Post-study Visit. Subjects that develop other causes of diarrhea associated with a negative *C. difficile* stool toxin test will not be considered a recurrence.

Modified Definition of Cure

In the modified definition of cure used in the sensitivity analysis, subjects who do not meet the criteria of 3 or fewer unformed stools for 2 consecutive days (maintained to the end of the end of therapy) will be considered failures regardless of any other data used at TOC. The sensitivity analysis for the primary efficacy analysis will be the same analysis

as described in the primary efficacy analysis, with the modified definition of cure rate as a response variable.

Definition of Time-to-Recurrence

Time-to-recurrence is defined as the time in days from the last date of dosing to the assessment date of recurrence. Time-to-Recurrence Formula: Recurrence Date minus Last Date of Dosing (in days).

Definition of Time-to-Resolution of Diarrhea

Time-to-resolution of diarrhea is defined as the time elapsing (in hours rounded up from minutes ≥30) from the start of treatment (time of first dose of study medication) to resolution (time of the last unformed bowel movement the day prior to the first of two consecutive days of ≤3 unformed bowel movements that are sustained through the end-of-therapy). During the daily subject interview, the subject will be queried regarding the continued passage of unformed stools. The subject will be reminded at study entry and during each interview to record the number and date/time of each passage and if the stool was unformed. The Investigator will record in the iCRF the date/time of the last unformed movement for the previous 24-hour period. The time (hours) from start of treatment to occurrence of resolution of diarrhea (the time (hours) of the last unformed bowel movement prior to the 48 hour window of 3 unformed bowel movements; sustained for the duration of treatment up to study day 10) will be compared between treatments for both the Modified Intent-to-Treat (mITT) and microbiologically-evaluable (ME) populations. Resolution of diarrhea will be assessed during an 8 to 12 day period utilizing the Subject Assessment data. Time-to-Resolution of Diarrhea Formula: 1st Resolution Date/Time minus 1st Dose of Study Medication Date/Time (in hours).

2. Diagnosis and Main Criteria for Inclusion:

Eligible subjects were male or female, 16 years of age or older, diagnosed with CDAD and had received no more than 24 hours of pretreatment with vancomycin or metronidazole (up to 4 doses in total) and no doses of other potentially effective treatments for CDAD (*e.g.*, oral bacitracin, fusidic acid, rifaximin, etc.).

CDAD was defined by:

1- Diarrhea: a change in bowel habits, with >3 unformed bowel movements (or >200 mL unformed stool for subjects having rectal collection devices) in the 24 hours before randomization, and
2- Presence of either toxin A or B of *C. difficile* in the stool within 48 hours of randomization.

Female subjects of childbearing potential were to use an adequate and reliable method of contraception (*e.g.*, barrier with additional spermicide foam or jelly, intrauterine device, hormonal contraception); postmenopausal females were considered to be beyond childbearing age if ≥1 year had passed since the cessation of menses. Subjects (both male

and female) must have agreed to avoid conception during treatment and for 4 weeks following the end of study treatment.

All subjects were required to sign an Informed Consent Form.

3. Analyses populations

The two main analyses sets for efficacy are the modified intent-to-treat (mITT) population and the Per Protocol (PP) population for cure.

The mITT population was defined as the group of randomized subjects with CDAD confirmed by >3 unformed bowel movements in the 24 hours prior to randomization and a positive toxin assay and who received at least one dose of study medication.

The PP population consisted of subjects in the mITT population who met the following criteria:

- Confirmed CDAD clinical diagnosis as stated above
- Met all inclusion criteria and met no exclusion criteria (unless deviations to either of these are documented and approved by the Sponsor)
- Sufficient course of therapy: subjects were required to have at least 3 complete days of treatment for failure and 8 complete days of treatment for cure, i.e., 6 active doses of fidaxomicin for a failure and 16 active doses of fidaxomicin for a cure, or 12 active doses of vancomycin for a failure and 32 active doses of vancomycin for a cure)
- Had an EOT clinical evaluation
- Did not have significant protocol violations including: Use of concomitant CDAD therapy or other drugs which could confound the assessment of efficacy, Other significant protocol violations, as judged by a blinded assessment prior to study unblinding

Note: Subjects with a positive toxin test within 96 hours (4 days) of randomization will be accepted into the mITT and microbiologically evaluable (ME) populations if they have not received more than 24 hours of *C. difficile* therapy as defined in the protocol and meet the other criteria for inclusion into these populations. Subjects that have received more than 24 hours of *C. difficile* therapy (e.g. metronidazole failure subjects) must have a positive toxin test within the 48-hour window prior to randomization.

Table 2.2: Analysis Populations

	Trial 003		Trial 004	
Population	Fidaxomicin	Vancomycin	Fidaxomicin	Vancomycin
Randomized	302	327	265	270
Randomized and Treated	300	323	264	260
mITT	289	307	253	256
PP	268	280	217	234

4. Statistical Methods:

The primary efficacy analysis compared the difference in clinical cure rates between treatment groups (fidaxomicin - vancomycin), using a two-sided 95% confidence interval (CI). Noninferiority of fidaxomicin to vancomycin was demonstrated if the lower limit of the CI was greater than the pre-specified non-inferiority margin of -10%. See Appendix A for the justification of the noninferiority margin.

The first secondary efficacy endpoint for this study is recurrence rate of CDAD by 28 days ±2 days after the last dose of study therapy. A two-sided 95% CI was computed for the difference in treatment recurrence rates.

Another secondary efficacy endpoint is global cure rate (percent of subjects who were cured and did not experience a recurrence) and time-to resolution of diarrhea. Treatment differences in global cure rate were evaluated using a 2-sided 95% CI and a z-test. Treatment differences in time-to-resolution of diarrhea were evaluated using Kaplan-Meier methods and the generalized Wilcoxon test.

It should be noted that global cure rate was an exploratory endpoint in trial 003 and a secondary endpoint in trial 004.

All statistical analyses were performed on the mITT population and the PP population.

It is potentially difficult to interpret the analyses for the recurrence endpoint because it can only be assessed in patients who were cures at the EOT assessment. This subgroup analysis is not protected by randomization so there is a concern that the patients could differ between treatment arms. In contrast, the analysis of the global cure rate is based on the mITT population and is protected by randomization. Therefore, it is felt to be more interpretable.

In order to maintain the overall error rate for testing of secondary endpoints, the following gate-keeping strategy is used as the statistical testing approach for secondary endpoints:

- If the noninferiority of fidaxomicin to vancomycin is demonstrated for mITT populations (1-sided alpha=0.025) and remain consistent in the PP population, the superiority comparison of treatments for recurrence rates will be made (two-sided alpha = 0.05).

-If the above treatment comparison for recurrence rates is statistically significant in favor of fidaxomicin for both the mITT and PP populations, the superiority comparison of treatments for global cure rate will be made using both the mITT and PP populations (two-sided alpha = 0.05).

The analysis of time-to-recurrence only includes subjects who were considered cured at the EOT visit. Subjects who never recurred during the follow-up period will be assigned a censored value of 1 at day 40. The survival function will be estimated by the Kaplan-Meier method. The comparison of survival curves of the treatment groups will be made using the generalized Wilcoxon test. Quartile estimates (25th, 50th (median), and 75th) and their two-sided 95% confidence intervals will be computed for both treatment groups. Summaries of time-to-recurrence for each treatment by initial strain of CDAD will also be presented for those subjects who experienced a recurrence. The time-to-recurrence analysis model will be accompanied by a graph of Kaplan-Meier estimated times.

The survival function for time-to-cure will be estimated by the Kaplan-Meier method. Subjects who complete required therapy, but do not show resolution of diarrhea during the treatment period, will be censored at Day 10. In addition, subjects who withdrew will be censored on day 10. [Note: For subjects who withdrew and record Subject Assessment data beyond their withdrawal date, the Time-to-Resolution of Diarrhea analysis will evaluate subjects up to the last recorded assessment day, not beyond Day 10.] Quartile estimates (25th, 50th (median), and 75th) and their two-sided 95% confidence intervals will be computed for both treatment groups.

Subgroup analysis on efficacy endpoints were conducted in the following: subject age, race, sex, baseline disease severity, country, presence of prior recurring CDAD, inpatient/outpatient status, stratum type and metronidazole failure status.

5. Handling missing values:

Cure Rate

Missing values in the investigator's classification of clinical cure or failure are replaced with the clinical failure classification.

Recurrence Rate

Missing values in the investigator's classification of recurrence or non-recurrence were replaced with a recurrence classification. There was an exception for missing values for subjects who were followed for more than 25 days after date of cure with complete Day 17, Day 24, and Day 31 Subject Assessments (7, 14, and 21 days after therapy, respectively) without indication of re-establishment of diarrhea; these were classified as non-recurrence.

Time-to-Recurrence

Missing values for date of cure ('Date of Assessment,' clinical response iCRF page) were replaced with 'Visit Date' on clinical response iCRF page; if the visit date was also missing, it was replaced with the date of the last dose.

Missing values for date of recurrence ('Date of Assessment,' recurrence iCRF page) were replaced with 'Visit Date' of recurrence iCRF page; if the visit data were also missing, they were replaced with the date discontinued from the study.

If a complete date for either date of cure or date of recurrence could not be imputed, the Time-to-Recurrence variable was not derived.

Global Efficacy

The global efficacy variable was derived using the classification for cure and recurrence after any imputation for missing values.

Summary of Results from Individual Studies

The following sections provide overviews of the individual results of the two Phase 3 trials (Trials 003 and 004). The primary analysis for the primary efficacy endpoint in both Trials 003 and 004 was performed in the mITT and PP co-primary populations.

Baseline patient demographic data for Trials 003 and 004 are summarized below:

Table 2.3: Baseline patient demographic data (mITT population)

	Trial 003			Trial 004		
	Fidaxomicin (N=287)	Vancomycin (N=309)	All subjects (N=596)	Fidaxomicin (N=252)	Vancomycin (N=257)	All subjects (N=509)
Sex, n (%)						
Female	164 (57.1)	169 (54.7)	333 (55.9)	148 (58.7)	162 (63.0)	310 (60.9)
Male	123 (42.9)	140 (45.3)	263 (44.1)	104 (41.3)	95 (37.0)	199 (39.1)
Race, n (%)						
White	252 (87.8)	267 (86.4)	519 (87.1)	232 (92.1)	238 (92.6)	470 (92.3)
Black	30 (10.5)	33 (10.7)	63 (10.6)	17 (6.7)	17 (6.6)	34 (6.7)
Asian	4 (1.4)	7 (2.3)	11 (1.8)	2 (0.8)	1 (0.4)	3 (0.6)
Other [a]	1 (0.3)	2 (0.6)	3 (0.5)	1 (0.4)	1 (0.4)	2 (0.4)
Age (yrs)						
N	287	309	596	252	257	509
Mean±SD	60.3±16.9	62.9±16.9	61.6±16.9	64.3±17.9	62.5±18.4	63.4±18.1
Median	61.0	64.0	63.0	67.5	65.0	66.0
Weight (kg)						
N	287	308	595	251	257	508
Mean±SD	78.1±24.2	76±21.3	77±22.8	71.44±20.7	70.88±19.8	71.15±20.2
Median	74.1	73.0	74.0	68.00	67.00	68.00
Range	36.4, 230.6	36, 242.3	36, 242.3	32.0, 231.6	32.8, 181.4	32.0, 231.6
Height (cm)						

N	287	308	595	251	256	507
Mean±SD	167.1±11.1	166.9±12.1	167±11.6	167.07±9.7	165.76±10.97	166.41±10.4
Median	167.0	167.6	167.6	166.00	165.00	165.10
Range	124, 193	129.5, 198	124, 198	146.0, 195.6	114.0, 208.0	114.0, 208.0
BMI(kg/m^2)[b]						
N	287	308	595	251	256	507
Mean±SD	27.9±8.1	27.3±7.4	27.6±7.8	25.5±6.30	25.7±6.7	25.6±6.3
Median	26.3	26.0	26.2	24.2	24.9	24.5
Range	15.9, 79.6	15.4, 83.6	15.4, 83.6	12.5, 63.8	12.8, 51.9	12.5, 63.8

[a] Other includes: American Indian and Alaska native.

[b] Calculated body mass index is defined as (weight in kg)/(height in meters)2.

BMI – body mass index; SD = standard deviation

Source: Applicant ISE Table 3.1-1

Table 2.4: Additional baseline patient demographic data (mITT population)

	101.1.C.003			101.1.C.004		
	Fidaxomicin (N=287)	Vancomycin (N=309)	All subjects (N=596)	Fidaxomicin (N=252)	Vancomycin (N=257)	All subjects (N=509)
Subject status, n (%)						
Inpatient	167 (58.2)	187 (60.5)	354 (59.4)	174 (69.0)	173 (67.3)	347 (68.2)
Outpatient	120 (41.8)	122 (39.5)	242 (40.6)	78 (31.0)	84 (32.7)	162 (31.8)
Stratum, n (%)						
No Prior Episode	239 (83.3)	255 (82.5)	494 (82.9)	212 (84.1)	221 (86.0)	433 (85.1)
Single Prior Episode	48 (16.7)	54 (17.5)	102 (17.1)	40 (15.9)	36 (14.0)	76 (14.9)
Daily Bowel Movements						
N	287	309	596	251	257	508
Mean ±SD	8.1±4.2	8.3±5.4	8.2±4.8	7.5±4.4	7.5±4.3	7.5±4.3
Median	7.0	6.0	7.0	6.0	6.0	6.0
Min, Max	4, 32	4, 50	4, 50	4, 30	4, 30	4, 30
Baseline disease severity[a], n (%)						
Mild	64 (22.3)	80 (25.9)	144 (24.2)	77 (30.6)	95 (37.0)	172 (33.8)
Moderate	111 (38.7)	106 (34.3)	217 (36.4)	82 (32.5)	73 (28.4)	155 (30.5)
Severe	112 (39.0)	123 (39.8)	235 (39.4)	90 (35.7)	88 (34.2)	178 (35.0)
Missing	0	0	0	3 (1.2)	1 (0.4)	4 (0.8)
C. difficile Toxin, n (%)						
Positive	287 (100)	309 (100)	596 (100)	252 (100)	257 (100)	509 (100)
Negative	0	0	0	0	0	0
CDI Indication, n (%)						
Diarrhea Alone	49 (17.1)	68 (22.0)	117 (19.6)	188 (74.6)	192 (74.7)	380 (74.7)
Diarrhea and Other Symptoms	238 (82.9)	241 (78.0)	479 (80.4)	64 (25.4)	65 (25.3)	129 (25.3)
Prior Use of CDI Antibiotics, n (%)						
Prior Use	128 (44.6)	139 (45.0)	267 (44.8)	225 (89.3)	220 (85.6)	445 (87.4)
No Prior Use	159 (55.4)	170 (55.0)	329 (55.2)	27 (10.7)	37 (14.4)	64 (12.6)
Metronidazole Failure, n (%)						
Yes	13 (4.5)	17 (5.5)	30 (5.0)	12 (4.8)	8 (3.1)	20 (3.9)
No	274 (95.5)	292 (94.5)	566 (95.0)	240 (95.2)	249 (96.9)	489 (96.1)

[a] Baseline disease severity categories are defined as: Mild CDI = 4-5 UBM/day or WBC <= 12,000/mm³; Moderate CDI = 6-9 UBM/day or WBC 12,001-15,000 mm³; Severe CDI = ≥ 10 UBM/day or WBC ≥15,001/mm³

Source: Applicant ISE Table 3.1-2

A summary of reasons for discontinuation of study drug in the randomized population is as follows:

Table 2.5: Reasons for Discontinuation of Study Drug

	101.1.C.003		101.1.C.004	
	Fidaxomicin (N=302)	Vancomycin (N=327)	Fidaxomicin (N=270)	Vancomycin (N=265)
Total who terminated early	22 (7.3)	32 (9.9)	45 (17.0)	34 (13.1)
Reason for early termination				
Adverse event	12 (4.0)	15 (4.6)	15 (5.6)	16 (6.0)
Subject choice	6 (2.0)	7 (2.1)	10 (3.7)	10 (3.8)
Clinical failure	NA	NA	8 (3.0)	3 (1.1)
Effective Concomitant CDI Therapy	0	5 (1.5)	0	0
Protocol violation	0	3 (0.9)	3 (1.1)	2 (0.8)
Non-compliance	2 (0.7)	1 (0.3)	8 (3.0)	3 (1.1)
Lost to follow-up	1 (0.3)	1 (0.3)	0	0
Treatment failure (less than 3 days of therapy)	1 (0.3)	0	0	0
Not having a robust enough response	NA	NA	1 (0.4)	0

NOTE: A subject can have multiple reasons for study termination. NA = not applicable (i.e. category was not included in the study as an option)

Source: Applicant ISE Table 3.1-3

III. PHARMACOLOGY-TOXICOLOGY

Cardiologic effects were minimal as tested in the hERG assay, telemeterized dogs (single 1 mg/kg intravenous dose), and in oral dog and monkey toxicology studies. No other respiratory, CNS or renal toxicities were identified in the safety pharmacology or general toxicology studies.

Absorption was variable and low by the oral route in most species tested. Metabolism by gut and intestinal enzymes in rats and dogs included the species formed by humans. Excretion was primarily via the fecal route. In dogs, less than 1% of the dose was excreted via the urine.

Toxicity studies of up to 3 months duration have been conducted by the oral and intravenous routes in rats, dogs and cynomolgus monkeys. All studies were conducted at the maximum feasible dose, but due to variable absorption, low solubility and presumed low bioavailability, studies by routes other than the clinical oral route were requested to better define the toxic potential of fidaxomicin. The initial one month oral gavage studies in rats and monkeys with labrasol as vehicle showed minimal toxicities at the maximum feasible dose of 90 mg/kg. Intravenous studies in rats for 14 days with 3 different vehicles were conducted. No fidaxomicin-related toxicities were noted at the maximum feasible doses (<4 mg/kg as an i.v. bolus). A 3 month oral capsule study in the dog showed no toxicity at the maximum feasible dose of approximately 1 g/kg/day.

Segment I and II reproductive toxicity studies were conducted in rats and rabbits. Fidaxomicin had no effects on fertility or development through implantation in the rat at

intravenous doses in 1% solutol HS15 of up to 6.3 mg/kg. In the rat by the intravenous route in 1% solutol HS15, when administered during the period of organogenesis, fidaxomicin had no effect on maternal or fetal parameters at the highest dose tested, 12.6 mg/kg. In the rabbit, the highest dose tested, 7.0 mg/kg, was a no observed adverse effect level (NOAEL) for both dams and offspring.

Fidaxomicin and its main metabolite, OP-1118, were negative for genotoxicity in the Ames bacterial assay. In the chromosomal aberration assay, fidaxomicin was positive, while OP-11118 was negative. Fidaxomicin was negative in the rat micronucleus assay.

IV. CLINICAL PHARMACOLOGY

Summary of Pharmacokinetics

Fidaxomicin is minimally absorbed from the gastrointestinal tract following oral (PO) administration due to poor permeability and poor solubility. Pharmacokinetic parameters of fidaxomicin and its major active metabolite, OP-1118, following a single PO dose of 200 mg are displayed in **Table 4-1**. Systemic exposure of metabolite OP-1118 was approximately 2 times that of the parent compound.

Table 4-1: Pharmacokinetic parameters of fidaxomicin and OP-1118 following single 200 mg PO dose of fidaxomicin (fasted) in healthy males

	C_{max} (ng/mL)	T_{max}[a] (h)	AUC_{0-t} (ng*h/mL)	$AUC_{0-\infty}$ (ng*h/mL)	$t_{1/2}$ (h)
Fidaxomicin					
N	14	14	14	9	9
Mean	5.20	2.00[a]	48.3	62.9	11.7
SD	2.81	(1.00-5.00)	18.4	19.5	4.80
OP-1118					
N	14	14	14	10	10
Mean	12.0	1.02[a]	103	118	11.2
SD	6.06	(1.00-5.00)	39.4	43.3	3.01

[a] T_{max} reported as median (minimum-maximum)

AUC_{0-t}, area under the concentration-time curve from time 0 to last measured concentration; $AUC_{0-\infty}$, area under the concentration-time curve from time 0 to infinity; C_{max}, maximum observed concentration; SD, standard deviation; T_{max}, time to maximum observed concentration; $t_{1/2}$, apparent elimination half-life

In Phase 3 patients treated with fidaxomicin 200 mg PO every 12 hours (Q12h) (**Table 4-2**), mean plasma concentrations of fidaxomicin and OP-1118 measured within the T_{max} window (i.e., 3-5 hours post-dose) were approximately 4-7 times that of C_{max} values in healthy subjects. Plasma concentrations of OP-1118, but not fidaxomicin, appeared to increase with repeat dose administration in Phase 3 patients.

Table 4-2: Detectable (>0.2 ng/mL) plasma concentrations at T_{max} for fidaxomicin and OP-1118 following 200 mg PO Q12h in fidaxomicin-treated patients from pooled Phase 3 trials

	Concentration at T_{max}[a] (ng/mL)			
	Fidaxomicin		OP-1118	
	Day 1	End-of-Therapy	Day 1	End-of-Therapy
N >LLOQ[b]	312	105	316	107
Mean	22.8	28.9	44.5	86.4

SD	26.7	32.8	50.4	129
Minimum	0.36	0.31	0.28	1.09
Maximum	197	191	363	871

[a] Samples collected at T_{max} were obtained within the 3-5 hour window post-dose
[b] Lower limit of quantification (LLOQ) for fidaxomicin and OP-1118 in plasma was 0.2 ng/mL

Absorption: When fidaxomicin was administered with a high-fat meal versus under fasting conditions, C_{max} of fidaxomicin and OP-1118 decreased by 21.5% and 33.4%, respectively, while AUC_{0-t} remained unchanged. This decrease in C_{max} is not clinically significant, and thus, fidaxomicin may be administered with or without food.

Distribution: Fidaxomicin is mainly confined to the gut following PO administration.

Metabolism: *In vitro* studies with human intestinal microsomes, liver microsomes, and hepatocytes indicate fidaxomicin is primarily transformed by hydrolysis at the isobutyrl ester to form the major active metabolite, OP-1118. CYP enzymes do not appear to play a significant role in the metabolism of fidaxomicin or formation of OP-1118.

OP-1118 possesses antibacterial activity that is weaker than the parent compound; its MIC_{90} against *C. difficile* is 32-fold higher than that of fidaxomicin.

Excretion: Fidaxomicin is mainly excreted in the feces. Following single doses of 200 and 300 mg in healthy adults (n=11), approximately 26.4% of the dose was recovered in stool as fidaxomicin and 66.2% as OP-1118.

Intrinsic Factors
Based on the Sponsor's analysis of Phase 3 patients, age (≥65 years versus <65 years), gender (male versus female), and renal impairment (creatinine clearance of 51-79 mL/min, 31-50 mL/min, and ≤30 mL/min) did not significantly impact plasma concentrations of fidaxomicin and OP-1118.

Extrinsic Factors
Enzyme-based drug interactions
Fidaxomicin did not inhibit or induce CYP enzymes at concentrations up to 10 µg/mL in *in vitro* studies with human liver microsomes and hepatocytes. However, the potential for drug-drug interactions via CYP enzymes prominent in the gut (CYP3A4 followed by CYP2C9 and CYP2C19) cannot be excluded based on estimated intestinal concentrations of fidaxomicin. Thus, an *in vivo* study was conducted using CYP probe substrates, midazolam, warfarin, and omeprazole.

Midazolam/Warfarin/Omeprazole: Co-administration of fidaxomicin 200 mg Q12h with a single-dose CYP cocktail of midazolam 5 mg (CYP3A4), warfarin 10 mg (CYP2C9), and omeprazole 40 mg (CYP2C19) in healthy males (n=24) showed no statistically significant effect on the pharmacokinetics of marker substrates and relevant metabolites. No dose adjustment of fidaxomicin or CYP substrates is warranted.

Transporter-based drug interactions

In vitro studies with Caco-2 cells indicate fidaxomicin is both a substrate and inhibitor of the efflux transporter, P-glycoprotein (P-gp).

Digoxin: Co-administration of fidaxomicin 200 mg Q12h with a single dose of digoxin 0.5 mg (known P-gp substrate) in healthy adults (n=14) had no clinically meaningful effect on the pharmacokinetics of digoxin. No dose adjustment of fidaxomicin or P-gp substrate is warranted.

Cyclosporine: Co-administration of cyclosporine 200 mg (known inhibitor of multiple transporters, including P-gp) and fidaxomicin 200 mg in healthy males (n=14) increased fidaxomicin and OP-1118 exposures by approximately 4-9 fold for C_{max} and 2-4 fold for $AUC_{0-\infty}$. Geometric mean C_{max} increased from 4.67 to 19.4 ng/mL for fidaxomicin and from 10.6 to 100 ng/mL for OP-1118. Geometric mean $AUC_{0-\infty}$ increased from 59.5 to 114 ng*h/mL for fidaxomicin and from 106 ng*h/mL to 438 ng*h/mL for OP-1118.

In pooled Phase 3 trials, clinical efficacy appeared to trend lower in patients who received known P-gp inhibitors during treatment, as rates of recurrence were higher and global cure rates were lower than those who did not receive P-gp inhibitors (**Table 4-3**).

Table 4-3: Fidaxomicin efficacy stratified by P-gp inhibitor use in pooled Phase 3 trials

	P-gp Inhibitor Use		Total
	No	Yes	
Clinical Cure			
PP	265/285 (93.0%)	181/200 (90.5%)	446/485 (92.0%)
mITT	281/312 (90.1%)	196/230 (85.2%)	477/542 (88.0%)
Recurrence			
PP-recurrence	23/238 (9.7%)	28/156 (18.0%)	51/394 (12.9%)
mITT-recurrence	31/281 (11.0%)	37/196 (18.9%)	68/477 (14.3%)
Global Cure			
PP	235/285 (82.5%)	146/200 (73.0%)	381/485 (78.6%)
mITT	250/312 (80.1%)	159/230 (69.1%)	409/542 (75.5%)

mITT, modified intent-to-treat population; mITT-recurrence; modified intent-to-treat recurrence population; PP, per-protocol population; PP-recurrence; per-protocol recurrence population

Concomitant use of P-gp inhibitors should be avoided while patients are receiving fidaxomicin, as local (i.e. gut) concentrations of fidaxomicin may be decreased and clinical efficacy may be compromised.

Clinical Dose Selection

The proposed clinical dose is fidaxomicin 200 mg PO Q12h for 10 days. In a dose-ranging Phase 2A trial, the regimen of 200 mg Q12h for 10 days provided the highest rates of clinical cure and symptom relief over lower doses without any increase in adverse events (**Table 4-4**).

Table 5-4: Fidaxomicin efficacy and safety in a dose-ranging Phase 2A trial

	50 mg Q12h × 10 days	100 mg Q12h × 10 days	200 mg Q12h × 10 days
Efficacy			
N, mITT	16	16	15
Clinical Cure	12/16 (75.0%)	13/16 (81.3%)	15/15 (100.0%)
Relief of Symptoms			
Relief	6/16 (37.5%)	8/16 (50.0%)	13/15 (86.7%)
No Relief	9/16 (56.3%)	6/16 (37.5%)	2/15 (13.3%)
Unknown	1/16 (6.3%)	2/16 (12.5%)	0/15 (0.0%)
Safety			
N	16	16	16
N with Adverse Event	4/16 (25.0%)	4/16 (25.0%)	1/16 (6.3%)

mITT, modified intent-to-treat population

V. EFFICACY

The FDA review results support the Applicant's claims for the endpoint of clinical cure and the endpoint of global cure. Although the numbers we report are slightly different than those of the applicant, our final conclusions are in agreement with the Applicant regarding noninferiority of fidaxomicin to vancomycin for the endpoint of clinical cure and superiority of fidaxomicin to vancomycin for the endpoint of global cure.

This section provides the FDA results for clinical cure and global cure. The results differ from the Applicant's results, and the reasons are explained below. However, our interpretation of the results is the same as that of the Applicant for these two endpoints. This section also presents results of additional sensitivity analyses motivated by differences in assessments. The final results of these sensitivity analyses were supportive of the Applicant's claims.

5.1 The reasons why our rates differ from those presented by the Applicant

The differences between the Agency's results and the Applicant's are due to some inconsistencies that we have identified during the review between the assessment of clinical cure or global cure by the investigators in the trial and other available information relating to drop out and diarrhea in the sample case report forms (CRFs).

Review of a random sample of 118 CRFs[1] identified a few subjects who were declared as cures or global cures by the Applicant although one or several of the following conditions were true: (1) Death during the study, (2) Concomitant medication treating CDAD during

[1] The FDA's DAIOP division requested that the Applicant submit a 10% random sample of the case report forms (CRFs) from studies 003 and 004. The CRFs were requested for the purpose of establishing consistency among the investigators in their conduct of the study, interpretation of the protocol, and accuracy in reporting of results.

treatment period or follow up, or (3) Recurrence assessment visit occurred early (before study day 31)[2].

The result from the sample of CRFs motivated a full search of all study subjects with similar possible inconsistencies. There are 13 subjects who were identified as cures by the Applicant with some inconsistencies and the breakdown by treatment and study is shown in Table 5.1. There are 85 subjects who were identified as global cures by the applicant with possible inconsistencies and the breakdown by treatment, study and reason of inconsistency is shown in Table 5.3. These inconsistencies motivated our sensitivity analyses described in the following subsections.[3]

5.2 Results for Cure

Table 5.1 shows the results for the endpoint of clinical cure at day 10. This table shows the Applicant's results as well as the results of the FDA analysis. The FDA analysis set changed the few observations with inconsistencies to failures. Subjects with inconsistencies are subjects considered cured by applicant although they either died before the end of treatment or had received concomitant medication treating CDAD during the treatment period. These are possible inconsistencies with the Applicant's assessment of cure because they could indicate treatment failure.

Table 5.1: Clinical Cure Rates at End of Treatment Visit

Applicant's Results				
Study	**003**		**004**	
Treatment (mITT)	**Fidaxomicin (N= 289)**	**Vancomycin (N = 307)**	**Fidaxomicin (N = 253)**	**Vancomycin (N = 256)**
Cure n/N (%)	255/289 (88%)	263/307 (86%)	222/253 (88%)	222/256 (87%)
Difference [1] 95% CI [2]	2.6% (-2.9%, 8.0%)		1.0% (-4.8%, 6.8%)	
FDA's Results (Sensitivity 1)				
Study	**003**		**004**	
Treatment (mITT)	**Fidaxomicin (N= 289)**	**Vancomycin (N = 307)**	**Fidaxomicin (N = 253)**	**Vancomycin (N = 256)**
Inconsistencies with Applicant's assessment of	0	5	5	3

[2] The protocol defined window for recurrence assessment visit is study day 36. However, as shown in the handling of missing values subsection in the clinical development section, the protocol allows for imputing missing recurrence assessments as non-recurrence if subjects were diarrhea free up to study day 31. Thus, study day 31 is the earliest protocol defined day to assess non-recurrence.

[3] Although our sensitivity analyses were not pre-planned in the protocol, they were developed after noticing the inconsistencies in the random sample and before the total tally of the inconsistencies across all subjects in the study.

cure [3]				
Cure n/N (%)	255/289 (88%)	258/307 (84%)	217/253 (87%)	219/256 (85%)
Difference [1] 95% CI [2]	4.2% (-1.4%, 9.7%)		2% (-5.9%, 6.4%)	

1. Difference = Cure Rate Fidaxomicin treatment arm – Cure Rate of Vancomycin treatment arm
2. 95% CI is using method recommended in Agresti and Caffo (2000) and Newcombe (1998)
3. Inconsistencies with applicant's assessment of cure are those subjects with outcome of cure by the applicant although these subjects died before day 10, or had taken concomitant medication treating CDAD during treatment period.

5.3 Modified Definition of Cure Results and Differences with Definition of Cure

The analysis of the modified definition of cure endpoint is the Applicant's pre-defined sensitivity analysis of the primary endpoint of cure. The results of this sensitivity analysis support the noninferiority claim of fidaxomicin to vancomycin, although the estimate for the treatment effect is lower with this endpoint.

The cure rates using the modified definition of cure in the mITT population are 79% in fidaxomicin arm and 80% in the vancomycin arm in trial 003 and 79% in both arms in trial 004. The 95% confidence for the difference in treatment effect (fidaxomin – vancomycin) is (-8%, 4.9%) in trial 003 and (-6.9%, 7.2%) in trial 004. Since the lower bound of the confidence interval in both studies is higher than -10%, this endpoint meets the non-inferiority margin as well.

As shown in

Table 5.2, the outcome of the modified cure endpoint agreed with the outcome of the cure endpoint for most subjects in both arms although the modified cure endpoint is more conservative. There is more agreement of outcomes from these two endpoints in study 003 (about 91% in both arms) than in study 004 (about 88% in both arms). Almost all of the differences between the outcomes from these two endpoints are for outcomes identified as success for cure but identified as failures for the modified cure.

Table 5.2: Differences between Cure and Modified Definition of Cure

Study 003				
Treatment (mITT)	**Fidaxomicin (N= 289)**		**Vancomycin (N = 307)**	
Cure\Modified	Modified Cure Failure	Modified Cure Success	Modified Cure Failure	Modified Cure Success
Cure-Failure	34	0	38	6
Cure-Success	27	228	22	241
Agreement				

n/N (%)	**262/289 (91%)**		**279/307 (91%)**	
Study 004				
Treatment (mITT)	**Fidaxomicin (N = 253)**		**Vancomycin (N = 256)**	
Cure\Modified	Modified Cure Failure	Modified Cure Success	Modified Cure Failure	Modified Cure Success
Cure-Failure	28	3	27	7
Cure-Success	24	198	26	196
Agreement n/N (%)	**226/253 (89%)**		**223/256 (87%)**	

5.3 Results for Global Cure

We first present the breakdown of identified inconsistencies by study and treatment and by reason for inconsistency. We then describe sensitivity analyses conducted by the Agency to address these inconsistencies.

The first sensitivity analysis treats all inconsistencies as failures. In the two other sensitivity analyses, we break the inconsistencies in two groups. The first group is the set of global failures from the agency's perspective and the second group is the set of cases with some doubt on whether global cure would have been achieved. The outcome of global cure for this second group of subjects is then considered "missing". The set of inconsistencies put in these two groups is different in sensitivity analysis 2 and 3. However, the two last sensitivity analyses use the same set of covariates to impute the missing values in the second group.

Identified Possible Inconsistencies

Three reasons for inconsistencies with Applicant's assessment of global cure were identified by the FDA review of the random sample of CRFs. The first reason is subject's death prior to study day 31. This is an inconsistency with assessment of global cure because the subject would have missed the earliest protocol allowed day for assessing non-recurrence. The second reason is subject's taking of concomitant medication treating CDAD either during the treatment phase or during the follow-up phase for recurrence. This is an inconsistency with assessment of global cure because the subject could have been prescribed this additional therapy due to treatment failure or suspected recurrence. The last reason is recurrence assessment visit occurring before study day 31. This is an inconsistency with assessment of global cure because subjects were followed for fewer days than the earliest protocol allowed day for assessing non-recurrence.

The breakdown of these inconsistencies by treatment group and study is shown in Table 5.3. Note that the total of inconsistencies is not the sum of each individual inconsistency since there is overlap in these categories. We see that the total number of inconsistencies with global cure is higher in the vancomycin group in both trials. This has an impact on

our sensitivity analyses as we will see that our sensitivity analyses show a larger estimated treatment effect of fidaxomicin compared to vancomycin.

Table 5.3: Potential Inconsistencies with Assessment of Global Cure

Study	003		004	
Treatment (Applicant's global cure)	Fidaxomicin (N= 215)	Vancomycin (N = 197)	Fidaxomicin (N = 194)	Vancomycin (N = 162)
Total Inconsistencies with Applicant's Assessement of Global Cure	18 (8%)	26 (13%)	18 (9%)	23 (14%)
Inconsistency due to death before study day 31	4	6	8	4
Inconsistency due to CDAD Concomitant Med during trt or follow up	12	18	12	13
Inconsistency due to recurrence visit before day 31	10	13	6	9

Sensitivity Analysis 1, Treating Inconsistencies as Failures

In this sensitivity analysis, we treat all inconsistencies as failures. Results are shown in Table 5.4. Because the inconsistencies occurred more often in the vancomycin arm, the estimate of treatment effect using this sensitivity analysis is larger than the one derived by applicant. Results of this sensitivity analysis demonstrate the superiority of fidaxomicin to vancomycin for Global Cure assessed at day 31.

Table 5.4: Global Cure Rate- Sensitivity Analysis Treating Inconsistencies as Failures

Study	003			004		
Treatment (mITT)	Fidaxomicin (N= 289)	Vancomycin (N = 307)	**Difference[1] (95% CI) [2]**	Fidaxomicin (N = 253)	Vancomycin (N = 256)	**Difference[1] (95% CI) [2]**
Global Cure (Applicant's results)	215/289 (74%)	197/307 (64%)	**10.2% (2.8, 17.5)**	194/253 (77%)	162/256 (63%)	**13.4% (5.4, 21.1)**

Inconsistencies Total	18/289 (6%)	26/307 (8%)		18/253 (7%)	23/256 (9%)	
Global Cure (FDA-Sensitivity 1)	197/289 (68%)	171/307 (56%)	**12.5% (4.7, 20)**	176/253 (70%)	139/256 (54%)	**15.3% (6.8, 23.4)**

1. Difference = Cure Rate Fidaxomicin treatment arm – Cure Rate of Vancomycin treatment arm
2. 95% CI is using method recommended in Agresti and Caffo (2000) and Newcombe (1998)

Sensitivity Analyses Using Multiple Imputation

The set of missing outcome in both sensitivity analysis 2 and sensitivity analysis 3 is different. The breakdown of what are considered global cure by the Applicant but failures by the FDA is shown in Table 5 for sensitivity analysis 2 and in Table 5.7 for sensitivity analysis 3.

The missing outcomes in each sensitivity analysis are imputed using multiple imputations method. We used the chained equation algorithm (van Buuren and Oudshoorn 2000, Raghunathan et al 2001) implemented in library MI in R (see Su et al (2009) and Gelman et al (2008)) to conduct the imputation and generate 25 imputed datasets. The estimate of the treatment effect as well as the confidence interval is derived from these imputed datasets.

In the imputation step, missing global cure rate outcomes are imputed using a logistic model predicting the probability of global cure with covariates of baseline characteristics, follow-up information for diarrhea and timing variables such as length of treatment. More specifically, we included the following variables in the logistic model: treatment assignment, study, study center, sex, race, age, weight, height, BMI, subject status, prior CDAD episodes, daily bowel movement at baseline or baseline disease severity, Diarrhea alone or other symptoms, prior use of CDAD antibiotics, metronidazole failure, number of study days in treatment phase, diarrhea at follow up visits after cure, serum albumin concentration (below 2.5 dl or not).

5.3.3.1 Sensitivity Analysis 2

In this sensitivity analysis (see Table 5), the global cure outcome of subjects who died before study day 31 or who had diarrhea during follow up period and received concomitant medication treating CDAD was changed to failure. All other inconsistencies identified in Table 5.3 were changed to missing. In addition, the outcome of global cure was changed to missing for all subjects who were cured at TOC and had a missing outcome for recurrence. Thus, this analysis corresponds to treating all non-cure, suspected CDAD recurrence or death as failures, whether or not the toxin is positive at the recurrence assessment. This analysis also sets all outcomes with incomplete information related to suspected CDAD recurrence as missing.

Results of this sensitivity analysis are shown in Table 5.6. We see that these results demonstrate superiority of fidaxomicin to vancomycin for Global Cure. The treatment effect estimate is higher for study 003 and about the same as the one reported by the Applicant for study 004. The confidence intervals in this sensitivity analysis account for the uncertainty in the estimate due to missingness. The percent of variation due to missingness is small; it is in the range of 2.8%-4.1% in each study.

Table 5.5: Missing Values and Disagreements in Sensitivity Analysis 2

Treatment	Fidaxomicin (N= 289)	Vancomycin (N = 307)	Fidaxomicin (N = 253)	Vancomycin (N = 256)
Disagreement: Applicant's Global Cure Success and FDA Global Cure Failure				
Total Disagreements	**8**	**12**	**12**	**10**
Deaths before study day 31	4	6	8	4
Concomitant Med to treat CDAD and Diarrhea	4	6	4	6
Missing Values: Applicant's Global Cure Success and FDA Global Cure Missing				
Total [1]	**10**	**14**	**6**	**13**
Missing Values: Applicant's Global Cure Failures and FDA Global Cure Missing [2]				
Cure and missing recurrence set as global cure failure by applicant because of missingness	**3**	**1**	**3**	**7**

1: The total includes those subjects with inconsistencies who are alive at study day 31 and either did not receive concomitant medication to treat CDAD or received concomitant medication to treat CDAD but did not have documented diarrhea.
2: These observations were cure but had missing information for recurrence and were assessed as global cure failure by applicant. Note that the only observation missing from clinical cure was a failure

Table 5.6: Global Cure Rate in Sensitivity Analysis 2

Study	**003**	**004**
Difference[1] 95% CI[2]	13.1% (5.0% - 21.2%)	13.3% (4.5%-22.0%)
Percent Total Variability Due to Missingness[3]	2.8%	4.1%

1. Difference = Global Cure Rate fidaxomicin treatment arm – Global Cure Rate of vancomycin treatment arm
2. 95% CI accounts for within imputed samples variability W and between imputed samples variability B
3. Percent of total variability due to missingness is the ratio (1+1/25)*B/ V, where V = W + (1+1/25)*B, B is the between imputed samples variation and W is the within imputed samples variation.

5.3.3.2 Sensitivity Analysis 3

The difference between this sensitivity analysis and sensitivity analysis 2 is that global cure outcomes of subjects who died before study day 31 are set to missing and imputed in this analysis whereas they are set to failures in sensitivity analysis 2.

In this sensitivity analysis (see Table 5.7), the global cure outcome of subjects identified as global cure by the Applicant although they had diarrhea during follow up period and received concomitant medication treating CDAD was changed to failure. All other inconsistencies identified in Table 5.3 were changed to missing. In addition, the outcome of global cure was set to missing for all subjects who were cured at test of cure and had a missing outcome for recurrence. This analysis corresponds to treating all non-cures and all suspected CDAD recurrences to failures, whether or not the toxin is positive at the recurrence assessment. This analysis also changes all outcomes with incomplete information related to suspected CDAD recurrence as missing, including those subjects who died before study day 31.

Results of this sensitivity analysis are shown in Table 5.8. We see that these results support the superiority of fidaxomicin to vancomycin for global cure. The treatment effect estimate is higher for study 003 and study 004 compared to the results reported by the Applicant. The confidence intervals in this sensitivity analysis account for the uncertainty in the estimate due to missingness. The percent of variation due to missingness is small; it is in the range of 3.8%-6.1% in each study.

Table 5.7: Disagreement and Missing Values in Sensitivity Analysis 3

Treatment	Fidaxomicin (N= 289)	Vancomycin (N = 307)	Fidaxomicin (N = 253)	Vancomycin (N = 256)
Disagreement: Applicant's Global Cure Success and FDA Global Cure Failure				
Concomitant Med to treat CDAD and Diarrhea	4	6	4	6
Missing Values: Applicant's Global Cure Success and FDA Global Cure Missing				
Total [1]	**14**	**20**	**14**	**17**
Missing Values: Applicant's Global Cure Failures and FDA Global Cure Missing				

Cure and missing recurrence (set to global cure failure by applicant)	**3**	**1**	**3**	**7**

1: The total include those subjects with inconsistencies who did not receive concomitant medication or received concomitant medication but did not have documented diarrhea

Table 5.8: Global Cure Rates- Sensitivity Analysis 3

Study	**003**	**004**
Difference[1] 95% CI[2]	13.1% (5.0%, 21.2%)	14.3% (5.5%, 23.0%)
Percent Total Variability Due to Missingness[3]	3.8%	6.1%

1. Difference = Global Cure Rate fidaxomicin treatment arm – Global Cure Rate of vancomycin treatment arm
2. 95% CI accounts for within imputed samples variability W and between imputed samples variability B
3. Percent of total variability due to missingness is the ratio (1+1/25)*B/ V, where V = W + (1+1/25)*B, B is the between imputed samples variation and W is the within imputed samples variation.

5.1.4 Subgroup analyses

The treatment effect for cure and global cure was consistent in most subgroups including different age groups and CDAD history subgroups. The only important exception is for virulent (BI) versus non-virulent (non BI) initial strains of C. *difficile*. Results for this subgroup are shown in

Table 5.9 for cure and Table 5.10 for global cure.

The treatment effect of fidaxomicin compared to vancomycin for the cure rate and global cure rate is smaller for the virulent strain than for the non-virulent strain in both studies and in the pooled analysis. The difference in treatment effects between the two subgroups is marginal for cure rates, but this difference is larger for global cure rates. The fidaxomicin arm does not have a superior outcome of global cure than vancomycin for the virulent strain, and the main factor driving this result are the differences in recurrence rates.

Table 5.9: Cure Rates for Different Initial Strains of C. *difficile*

Study 003			
	Fidaxomicin	**Vancomycin**	**Difference[1] (95% CI) [2]**
Missing	77/87 (88%)	77/94 (82%)	6.6% (-4.0%, 16.9%)
Virulent (BI)	60/76 (79%)	66/82 (80%)	-1.5% (-14.2%, 10.9%)
Non-virulent (non BI)	118/126 (94%)	120/131 (92%)	2.0% (-4.7%, 8.8%)
Study 004			
	Fidaxomicin	**Vancomycin**	**Difference[1] (95% CI) [2]**
Missing	48/57 (84%)	66/75 (88%)	-3.8% (-16.6%, 8.0%)
Virulent (BI)	54/65 (83%)	50/60 (83%)	-0.2% (-13.4%, 13.2%)
Non-virulent (non BI)	120/131 (92%)	106/121 (88%)	4.0% (-3.6%, 11.9%)
Pooled 003 and 004 studies			
	Fidaxomicin	**Vancomycin**	**Difference[1] (95% CI) [2]**
Missing	125/144 (87%)	143/169 (85%)	2.2% (-5.8%, 9.9%)
Virulent (BI)	114/141 (81%)	116/142 (82%)	-0.8% (-10.0%, 8.2%)
Non-virulent (non BI)	238/257 (93%)	226/252 (89%)	2.9% (-2.1%, 8.0%)

1. Difference = Cure Rate Fidaxomicin treatment arm – Cure Rate of Vancomycin treatment arm
2. 95% CI is using method recommended in Agresti and Caffo (2000) and Newcombe (1998)

Table 5.10: Global Cure Rates for Different Initial Strains of CDI

Study 003			
Initial Strain of CDI	**Fidaxomicin**	**Vancomycin**	**Difference[1] (95% CI) [2]**
Missing	66/87 (76%)	58/94 (61%)	14.1% (0.6%, 26.9%)
Virulent (BI)	66/76 (58%)	52/82 (63%)	-5.5% (-2.0%, 9.5%)
Non-virulent (non BI)	105/126 (83%)	87/131 (66%)	16.9% (6.3%, 27.0%)

Study 004			
Initial Strain of CDI	**Fidaxomicin**	**Vancomycin**	**Difference[1] (95% CI) [2]**
Missing	43/57 (75%)	54/75 (72%)	3.4% (-11.9%, 17.9%)
Virulent (BI)	42/65 (65%)	31/60 (52%)	12.9% (-4.2%, 29.2%)
Non-virulent (non BI)	109/131 (83%)	77/121 (64%)	19.6% (8.7%, 30.0%)
Pooled 003 and 004 studies			
Initial Strain of CDI	**Fidaxomicin**	**Vancomycin**	**Difference[1] (95% CI) [2]**
Missing	109/144 (76%)	112/169 (66%)	9.4% (-0.7%, 19.1%)
Virulent (BI)	86/141 (61%)	83/142 (58%)	2.5% (-8.8%, 13.8%)
Non-virulent (non BI)	214/257 (83%)	164/252 (65%)	18.2% (10.6%, 25.5%)

1. Difference = Cure Rate Fidaxomicin treatment arm – Cure Rate of Vancomycin treatment arm
2. 95% CI is using method recommended in Agresti and Caffo (2000) and Newcombe (1998)

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VI. SAFETY

The NDA database included 676 patients who received at least one dose of fidaxomicin and 593 patients who received comparator: 583 patients received vancomycin and 10 patients received placebo. The safety population includes 564 patients in the fidaxomicin group and 583 patients in the vancomycin group who received at least 1 dose of study drug and had at least 1 safety assessment after dosing in phase 3 trials.

Exposure

In phase 3 trials, the mean duration of exposure to fidaxomicin 400 mg and to vancomycin 500 mg was 10.2 days. The majority of subjects in both the fidaxomicin 400 mg (82.1%) and vancomycin (80.4%) groups were exposed to study drug for 10 to 11 days. In the phase 1 and 2 trials, subjects were exposed to study drug for a mean of 6.8, 5.5, and 5.9 in the fidaxomicin 100-200 mg, fidaxomicin 300 mg, and fidaxomicin 450 mg groups, respectively.

Deaths

The incidence of treatment-emergent adverse events (TEAEs) resulting in death was similar for subjects in the fidaxomicin and vancomycin groups. There were 74 deaths in phase 3 trials with 36 (6.4%) deaths in the fidaxomicin and 38 (6.5%) deaths in vancomycin group. There was one death in Phase 2A trial. The majority of deaths in phase 3 trials occurred during first 30 study days with 26 and 29 deaths in the fidaxomicin and vancomycin groups, respectively. During first 10 study days, there were 6 and 14 deaths in the fidaxomicin and vancomycin groups, respectively.

The MedDRA system organ classes (SOCs) with the highest incidence of TEAEs resulting in death reported in the fidaxomicin 400 mg and vancomycin 500 mg groups, respectively, were infections and infestations (2.0% and 1.9%); respiratory, thoracic, and mediastinal disorders (1.6% and 0.5%); and neoplasms benign, malignant and unspecified (0.9% and 0.5%). The TEAEs resulting in death reported at the highest incidences in the fidaxomicin 400 mg group were respiratory failure in 4 (0.7%) subjects; and pneumonia and sepsis in 3 (0.5%) subjects. The TEAEs resulting in death reported at the highest incidences in the vancomycin 500 mg group were sepsis in 4 (0.7%) subjects; and multi-organ failure in 3 (0.5%) subjects.

All of the TEAEs leading to deaths were assessed by the Investigator as not related or unlikely related to study drug. The reviewer deemed that nine deaths in Phase 3 trials could possibly be related to study drug; five deaths occurred in the fidaxomicin group (subjects 003-016005, 004-025008, 004-057022, 004-088026, 004-154002, and 004-172019) and four deaths occurred in the vancomycin group (patients 003-010029, 003-011033, 004-049002, and 004-178004). Deaths in both groups were attributed to possible lack of efficacy.

The majority of deaths in phase 3 trials occurred during the first 30 study days with 26 and 29 deaths in the fidaxomicin and vancomycin groups, respectively. During first 10 study days, there were 6 and 14 deaths in the fidaxomicin and vancomycin groups, respectively. None of the deaths within the first 10 days in the fidaxomicin group deemed related to study drug. Two deaths in vancomycin group were determined to be possibly related to study drug by the reviewer.

Thirteen deaths, seven in the fidaxomicin and six in vancomycin groups, were unlikely to be related to study drug. The other deaths were deemed not related to study drug but to the underlying medical conditions. The death in the Phase 2 trial was determined to be not related to study drug. Table 6.1 provides a list of the patient whose deaths were deemed to be possibly related to study drug.

Table 6.1 Reviewer Defined Subjects Whose Deaths Could Possibly Be Related to Study Drug.

Subject ID	Age Sex	Days on Study Drug	Study Day of Death	Cause of death Event preferred term	Relationship to Study Drug		
					Sponsor-Defined	Reviewer - Defined	Possible Toxicity and/or Lack of Efficacy
Study 101.1.C.003 Fidaxomicin							
016005*	79F	11	55	Sepsis syndrome / Pseudomembranous colitis	Not related	Possibly related	Lack of efficacy
Study 101.1.C.003 Vancomycin							
010029*	74F	8	10	Septic shock	Not related	Possibly related	Lack of efficacy
011033*	76M	4	11	Sepsis	Unlikely related	Possibly related	Lack of efficacy
Study 101.1.C.004 Fidaxomicin							
025008*	81F	6	16	Respiratory failure / Megacolon	Not related	Possibly related	Lack of efficacy
057022*	89M	5	12	Gastrointestinal perforation	Unlikely related	Possibly related	Lack of efficacy
154002*	72M	4	23	Renal Failure / Pseudomembranous colitis	Not related	Possibly related	Lack of efficacy
172019*	83M	11	31	Sepsis / Clostridium difficile sepsis	Not related	Possibly related	Lack of efficacy
Study 101.1.C.004 Vancomycin							
049002*	85F	7	8	Pneumonia	Not related	Possibly related	Lack of efficacy
178004*	50M	5	33	Septic shock	Not related	Possibly related	Lack of efficacy

* Case narratives are provided

Subject 003-016005 / Fidaxomicin

This 79-year old female was declared a clinical failure after receiving 11 days of study therapy due to persistent diarrhea and pseudomembranous colitis found on sigmoidoscopy. The patient received repeated courses of intravenous metronidazole and oral vancomycin but continued to have diarrhea and findings consistent with pseudomembranous colitis on colonoscopy. She subsequently developed acute renal failure, septic shock and died on study day 55.

Medical reviewer comments: In this case of refractory C. difficile infection, the lack of efficacy of the study drug could possibly be related to the outcome of death since the patient failed initial therapy of CDAD and finally died from complications of C. difficile infection.

Subject 004-025008 / Fidaxomicin

This 81-year-old woman was switched to intravenous metronidazole and oral vancomycin due to treatment failure and progression of CDAD on study day 6. On study day 9 the patient underwent subtotal colectomy for toxic megacolon. The patient's condition continued to worsen and she expired on study day 16.

Medical reviewer comments: This subject failed initial therapy of CDAD which resulted in toxic megacolon and death. The outcome of death could be possibly related to the study drug due to lack of efficacy.

Subject 004-057022 / Fidaxomicin

This 89-year-old male was declared a clinical failure after a 5-day course of study drug due to persistent diarrhea. The patient was started on oral vancomycin and intravenous metronidazole. On study day 9 the patient was diagnosed with bowel perforation. It was concluded that the patient was not fit for surgery. The patient's conditions continued to deteriorate and the patient expired on study day 12. Autopsy was not performed.

Medical reviewer comments: This patient died from complications of C. difficile infection after he had failed study therapy. The outcome of death could be possibly related to the study drug due to lack of efficacy.

Subject 004-154002 / Fidaxomicin

This 72-year-old male on chronic hemodialysis was changed to oral vancomycin and intravenous metronidazole after four days of study therapy due to continuous diarrhea, signs of significant colitis on computed tomography (CT) scan, and hypotension. The subsequent course was complicated by myocardial infarction. On study day 22 the patient decided to discontinue hemodialysis and subsequently died.

Medical reviewer comments: The initial failure to control CDAD may have complicated clinical course of this patient and contributed to the outcome of death. Thus, the study drug may possibly be related to this patient's death due to lack of efficacy.

Subject 004-172019 / Fidaxomicin

This 83-year old male was initially successfully treated with an 11-day course of study drug. On study day 26 the patient has a recurrence of CDAD. He was hospitalized in a non-affiliated facility with severe *C. difficile* colitis, hypotension and coma and died on study day 31.

Medical reviewer comments: This patient died from sepsis seemingly related to a severe recurrent C. difficile infection. The outcome of death could be possibly related to the study drug due to lack of efficacy.

Subject 003-010029 / Vancomycin

This 74-year-old white female study medication was stopped on study day 8 due to treatment failure. The subject was started on oral metronidazole and oral vancomycin. The patient's conditions continue to worsen and she expired from septic shock on study day 10.

Medical reviewer comments: The outcome of death could be possibly related to the study drug due to lack of efficacy. It has to be considered, however, that this patient had a severe concurrent disease.

Subject 003-011033 / Vancomycin

This 76-year-old male was declared a clinical failure on study day 4 when he developed hypotension, respiratory failure, and required intubation. The subject continued to have diarrhea by that time. CDAD therapy was changed to vancomycin via nasogastric tube and intravenous metronidazole. The patient's conditions continued to worsen and he died on study day 11 from septic shock.

Medical reviewer comments: The outcome of death could be possibly related to the study drug due to lack of efficacy. The patient failed initial CDAD therapy which may have contributed to progression of sepsis resulting in septic shock and death.

Subject 004-049002 / Vancomycin

This 85-year-old female had continuous diarrhea and developed hypotension, respiratory failure, oliguria, and metabolic acidosis on study day 6. On study day 7 the patient was withdrawn form the study, changed to palliative care and then died on study day 8.

Medical reviewer comments: This patient continued to have persistent symptoms of C. difficile infection resulting in the deterioration of her conditions. The outcome of death could be possibly related to the study drug due to lack of efficacy.

Subject 004-178004 / Vancomycin

This 50-year-old-male with hepatitis C, cirrhosis, portal hypertension and hepatic encephalopathy had a recurrence of CDAD by study day 27, associated with worsening of liver insufficiency and acute renal failure. The patient developed septic shock and died on study day 33.

Medical reviewer comments: The death of this patient could possibly be related to lack of efficacy of vancomycin resulting in recurrence of CDAD and subsequent death.

Serious Adverse Events

The incidence of treatment-emergent serious adverse events (SAEs) in phase 3 trials was 25.7% and in 23.2% in the fidaxomicin and vancomycin group, respectively. SAEs that occurred at a higher incidence in the fidaxomicin arm compared to vancomycin group included gastrointestinal (GI) hemorrhage, megacolon and decreases in WBC counts in the fidaxomicin. The incidence of selected adverse events according to MedDRA system organ class (SOC) and preferred term is presented in Table 6.2.

Table 6.2 Selected Serious Adverse Events: Safety Population in Phase 3 trials.

Preferred Term	Fidaxomicin N=564 n(%)	Vancomycin N=583 n (%)
No of subjects with ≥ 1 SAE	**145 (25.7)**	**135 (23.2)**
Gastrointestinal hemorrhage / Diarrhea hemorrhagic	6 (1.1)	1 (0.2)
Upper gastrointestinal hemorrhage	0	1 (0.2)
Esophageal varices hemorrhage	0	1 (0.2)
Megacolon	3 (0.5)	0
Colitis	2 (0.4)	0
Gastrointestinal perforation / Large intestine perforation	1 (0.2)	2 (0.3)
Leukopenia /Neutropenia / Granulocytopenia	8(0.7)	2 (0.3)
Lymphocyte count decreased	4 (0.7)	1 (0.2)
Ileus / Ileus paralytic	0	2 (0.3)
Overdose / Duodenal perforation	1 (0.2)	0
Vomiting / Nausea	3 (0.5)	3 (0.5)
Sepsis / Sepsis Syndrome / Septic shock	9 (1.6)	7 (1.2)
Cleft palate	1 (0.2)	0
Intra-uterine death	1 (0.2)	0
Pregnancy	1 (0.2)	0
Anaphylactic reaction	1 (0.2)	0

6.1.1 Gastrointestinal hemorrhage

Twenty fidaxomicin-treated subjects and 10 vancomycin-treated subjects were reported by the Sponsor to have AEs related to GI hemorrhage in the phase 3 trials (Table 6.3). Of note, the reviewer found two more vancomycin-treated subjects with clinical

presentations consistent with GI hemorrhage. In addition, one fidaxomicin patient in phase 2 trial had an adverse event of GI hemorrhage.

The overall severity of GI hemorrhage appears to be somewhat greater in the fidaxomicin group. Two fidaxomicin patients stopped study drug due to GI hemorrhage and one patient in the fidaxomicin group died from GI hemorrhage. In contrast, there were no discontinuations or deaths related to GI hemorrhage in the vancomycin group.

Table 6.3 Treatment-Emergent Adverse Events Related to GI Hemorrhage

	Fidaxomicin (N=564) n (%)	Vancomycin (N=583) n (%)
Phase 3 trials		
Number Of Subjects With >=1 TEAE	20 (3.5%)	10 (1.7%)
Diarrhea Hemorrhagic	5 (0.9%)	0
Gastrointestinal Hemorrhage	5 (0.9%)	1 (0.2%)
Hematemesis	0	1 (0.2%)
Hematochezia	7 (1.2%)	1 (0.2%)
Hemorrhoidal Hemorrhage	1	1 (0.2%)
Esophageal Varices Hemorrhage	0	1 (0.2%)
Rectal Hemorrhage	2 (0.4%)	3 (0.5%)
Upper Gastrointestinal Hemorrhage	0	1 (0.2%)
Occult Blood Positive	0	1 (0.2%)
Phase 2 trial (48 subjects)		
Gastrointestinal Hemorrhage	1 (2.1%)	NA

Source: Sponsor's table 14.3.1.10.2A, edited

In the fidaxomicin group, 12 episodes of gastrointestinal hemorrhage occurred after completion of study drug and 9 on study drug. The more severe events tended to occur weeks after study drug dosing. Clinical presentation was most consistent with lower GI hemorrhage in 16 cases, upper GI hemorrhage in 2 cases; the source of hemorrhage was difficult to ascertain in 3 cases. Several of these events consisted of a single bloody bowel movement with rapid resolution and were not considered clinically significant. All of the GI bleeding events for fidaxomicin were assessed by the investigator as not related or unlikely related to fidaxomicin but rather more likely to be associated with some other underlying condition. The reviewer could not rule out possible association between GI hemorrhage and the study drug in 11 cases.

In the vancomycin group, hemorrhage occurred after study drug was completed in eight cases. The presentation was most consistent with lower GI hemorrhage in 5 cases and upper GI hemorrhage in 4 cases. The reviewer could not rule out possible association between GI hemorrhage and the study drug in 4 cases.

In conclusion, there is a numerical imbalance in the incidence of GI hemorrhage in the fidaxomicin group compared with vancomycin group. It has to be noted that neither GI

hemorrhage nor any changes in the GI tract were reported in the preclinical animal studies.

Overdose / Duodenal Perforation

There was a case of study drug overdose in the fidaxomicin group followed by duodenal perforation (subject 003-137011). This 64-year-old male with no prior history of peptic ulcer disease received all four doses of study drug at once on day 3 of study drug therapy. Past medical history was significant for renal cell cancer with spinal metastases, coronary artery disease, hyperlipidemia and hypertension. Concomitant medications included enteric coated aspirin, atorvastatin, metoprolol, and intravenous potassium chloride. The same day the patient was withdrawn from the study and started on vancomycin 125 mg PO QID.

The next day after the overdose, on study day 4, the patient developed hypotension, anuria, respiratory failure and required mechanical ventilation. On study day 5 the patient remained in critical conditions with elevation of WBC to 33 X 10^9/L. The patient was taken to the operating room and diagnosed with perforated duodenal ulcer. Subsequently, his conditions slowly improved and on study day 18 the patient was transferred to the general ward.

Megacolon

Three subjects in the fidaxomicin group and none in the vancomycin group were reported to develop megacolon. Two cases of megacolon in the fidaxomicin group were determined to be possibly related to study drug by the medical reviewer (subject ID 003-048003 and 004-025008). The study drug in these subjects was discontinued due to treatment failure after 3 and 6 days of therapy, respectively. Both subjects then underwent colectomy. The subject 003-048003 recovered and the subject 004-035008 died on study day 16. The third case of megacolon in the fidaxomicin group, subject 003-010002, was deemed unlikely related to study drug. This subject received only two doses of study drug before his conditions worsened and urgent colectomy was performed the next day.

Decrease in White Blood Cell Count

More subjects in the fidaxomicin than in vancomycin group in phase 3 trials were found to have decreases in white blood cell count. Eight (1.4) versus 2 (0.3%) subjects developed adverse events described with the preferred terms of granulocytopenia, leukopenia, and neutropenia in the fidaxomicin and vancomycin group, respectively. No abnormal shifts in hematology values were reported for subjects in the fidaxomicin 100-200 mg group.

The review does not reveal an apparent reason for a decrease in WBC in fidaxomicin treated patients. This could be related to an increase in sepsis-related complications in the fidaxomicin group. Importantly, no bone marrow toxicity was observed in the preclinical

studies. However, negative animal data can not exclude the possibility of bone marrow toxicity. The Sponsor indicates that more fidaxomicin than vancomycin subjects in phase 3 trials received concomitant anti-neoplastic/immunomodulating agents (11.9% vs. 8.2%, respectively) which may partially explain reductions in WBC parameters in the fidaxomicin group.

Pregnancy

There was a case of pregnancy associated with intrauterine death and congenital defects in a fidaxomicin patient in study 003 (subject 003-009021). This 19-year-old female with precursor B cell acute lymphocytic lymphoma had a negative serum pregnancy test on study day 1 (b) (6). Three weeks prior to enrollment the patient received vincristine and methotrexate. Two weeks prior to enrollment she received ceftazidime and intravenous clindamycin for neutropenic fever and skin infection. Her last menstrual period occurred two weeks prior to study entry.

The patient was discharged on study day 6 and completed the course of study drug through study day 11 (b) (6) with resolution of CDAD. The other medications received during the admission included Nystatin, chlorhexidine orally for esophagitis, sucralfate, Pepcid, and Benadryl. At a follow-up visit on study day 25 (b) (6) a serum pregnancy test was positive. The patient decided to stop treatment for lymphoma and continue with pregnancy.

The subject's first trimester ultrasound on (b) (6) showed 5 live intrauterine fetuses with normal growth. An ultrasound on (b) (6) revealed four live and one fetus without cardiac pulsation, consistent with fetal demise. On (b) (6), at 18 weeks of pregnancy, the patient spontaneously delivered one fetus. An ultrasound showed that 1 of the remaining 4 fetuses had no heartbeat. On (b) (6) the patient delivered 3 live and 1 deceased fetuses. One female fetus was found to have a cleft palate and extensive autolysis of organs.

Medical reviewer deems that the association of fetal death and congenital anomalies and the study drug in this patient are possible, but uncertain. Based on the timeline of the events, the patient may have become pregnant while receiving the study drug. The patient also received methotrexate and vinciristine, which are known to cause fetal harm, 3 weeks prior to enrollment and probably 4 weeks prior to pregnancy.

Anaphylactic reaction

There was one case of anaphylactic reaction in the fidaxomicin group in the phase 3 trials which deemed to be not related to study drug. This 66-year-old male was given subcutaneous injection of vitamin K and fresh frozen plasma for elevated INR on study day 2. In 20-30 minutes after the initiation of treatment, the patient developed nausea, vomiting, and hypotension requiring vasopressors. The symptoms resolved in 3.5 hours. The patient continued to receive the study drug and completed an 11-day course of study treatment with an outcome of cure. The reviewer deems that the anaphylactic reaction

was more likely related to frozen plasma or vitamin K rather than to study drug. Moreover, subsequent uneventful rechallenge with fidaxomicin argues against its relationship to the anaphylactic reaction.

Dropouts and/or Discontinuations

The rates of dropouts were similar in the fidaxomicin and vancomycin groups in the phase 3 trials. There were 94 (16.7%) and 103 (17.7%) subjects in the fidaxomicin and vancomycin groups, respectively, who discontinued phase 3 trials (Table 7.5). Clinical failure as a reason for discontinuation was determined by the Sponsor only for study 101.1.C.004 where 8 (3%) subjects in the fidaxomicin and 3 (1.1%) in the vancomycin group discontinued the study for this reason. The reviewer analyzed discontinuations due to clinical failure for both phase 3 trials. According to the reviewer analysis, there were more subjects in the fidaxomicin group than in the vancomycin group who discontinued phase 3 trials due to clinical failure – 13 (2.3%) and 5 (0.8%), respectively.

According to the reviewer analysis, more vancomycin treated subjects when compared to fidaxomicin treated subjects discontinued the studies due to adverse events during the treatment phase – 36 (6.1%) and 22 (3.8%), respectively. During the follow-up phase, 17 (2.9%) fidaxomicin subjects and 21 (3.7%) vancomycin subjects discontinued the study drug due to adverse events.

Vomiting was the TEAE most frequently leading to study drug discontinuation for fidaxomicin subjects. Discontinuation of dosing due to vomiting occurred in 0.5% of both the fidaxomicin 400 mg and the vancomycin 500 mg groups.

There was an event of drug overdose that was deemed definitely related to study drug. The reviewer determined that ten adverse events in the fidaxomicin group could possibly be related to study drug. Seven events deemed to be due to possible toxicity included GI hemorrhage (2 subjects), vomiting (2 subjects), abnormal liver function tests (1 subject), lymphocytic colitis (1 subject), and hallucinations (1 subject). The case of liver function abnormalities did not meet Hy's law criteria.

There were five adverse events in the vancomycin group that resulted in the discontinuation from the study deemed to be possibly related to study drug by the reviewer. Three adverse events – erythema, rash and nausea were attributed to possible toxicity and the other two events were attributed to lack of efficacy.

Table 6.5 Subject Disposition and Reasons for Discontinuation in Phase 3 trials

	101.1.C.003		101.1.C.004	
	Fidaxomicin (N=302)	Vancomycin (N=327)	Fidaxomicin (N=270)	Vancomycin (n=265)
No. of subjects who were enrolled and randomized	302	327	270	265
No. of subjects who were randomized and received study medication	300	323	264	260

No. of subjects with recurrence or completing the post study visit	265	275	227	221
No. of subjects prematurely withdrawn from the study during the treatment phase; reason for early termination	22 (7.3)	32 (9.8)	45 (16.7)	34 (12.8)
Adverse event	10 (3.3)	22 (6.8)	12 (4.5)	14 (5.3)
Clinical failure	8 (2.7)	3 (0.9)	5(1.9)	2 (0.8)
Treatment failure (less than 3 days of therapy)	2 (0.7)	2 (0.6)	1 (0.4)	1 (0.4)
Other*	2(0.7)	5 (1.5)	27 (10.2)	17 (6.5)
No. of subjects prematurely withdrawn from the study during the follow-up phase; reason for withdrawal	15 (5)	20 (6.1)	12 (4.4)	17 (6.4)
Adverse event	9 (3.0)	8 (2.4)	12 (3.0)	9 (3.5)
Other	6	12	0	8
No. of subjects completing entire study (cure + recurrence)	265 (87.7)	275 (84.1)	214 (79.3)	214 (80.7)

*Other category included: subject choice, effective concomitant CDI therapy, protocol violation, non-compliance, lost to follow-up, and reason not specified.

Treatment-Emergent Adverse Events

The incidence of TEAEs was similar for subjects in the fidaxomicin (68.3%) and vancomycin (65.5%) groups in the phase 3 trials. The overall incidence of mild, moderate, and severe TEAEs was similar for the fidaxomicin and vancomycin groups (28.4% vs. 29.3% for mild, 20.7% vs. 19.4% for moderate, and 19.1% vs. 16.8% for severe, respectively).

Fidaxomicin Plasma Levels

Plasma levels of fidaxomicin and its metabolite OP-1118 were higher in subjects in phase 3 trials than in healthy volunteers. Phase 3 trial subjects had levels of fidaxomicin and OP-1118 up to 237 ng/mL and 871 ng/mL, respectively whereas no healthy volunteers receiving fidaxomicin had fidaxomicin or OP-1118 plasma levels above 50 ng/mL Plasma fidaxomicin levels were approximately 2 times higher in older (≥65 years) subjects than younger (<65 years) subjects.

There was a higher incidence of TEAEs for almost all SOCs in subjects with high plasma levels (≥150 ng/mL) when compared with subjects with low plasma levels (<150 ng/mL). Subjects with higher plasma levels vs. lower plasma levels were older (mean age of 74.6 vs. 60.6), were more frequently inpatients (92.7% vs. 62.5%), more frequently had severe CDAD (46.3% vs. 21.5%), more frequently had lower baseline albumin [<2.5 mg/dL] (43.2% vs. 17.0%), and more frequently had higher baseline creatinine [≥1.5 mg/dL] (29.7% vs. 11.3%).

A possible explanation for these findings is that more severe CDAD may be associated with poor intestinal integrity and higher systemic absorption, leading to higher fidaxomicin plasma levels. It has to be noted that no observed adverse effect levels were seen in toxicology studies at fidaxomicin exposure levels at least 100-fold above the human plasma concentrations at the therapeutic dose.

Clinical Laboratory Evaluations

No clinically significant difference in clinical chemistry parameters was observed between fidaxomicin and vancomycin groups. A higher incidence of decrease in WBC count has been discussed in other sections of the briefing document.

Safety in Subgroups

The Applicant explored the subgroups of age, gender, race, country, baseline CDAD severity, baseline number of unformed bowel movements (UBM), *C. difficile* strain type (BI strain vs. non-BI strain), inpatient versus outpatient status, renal insufficiency for potential safety differences. The decrease in WBC indices in the fidaxomicin group was more pronounced in subjects ≥ 65 years, non-White subjects, and subjects with more severe disease. A greater proportion of fidaxomicin treated subjects with more severe disease had abnormally low bicarbonate (7.3% vs. 2.3%) which may reflect severity of diarrhea and metabolic acidosis in these subjects. No clinically significant differences in the overall incidence of TEAEs were observed within subpopulations with different levels of renal insufficiency. Otherwise, no consistent clinically relevant adverse trends were observed in the fidaxomicin treatment group compared with the vancomycin group.

Cardiac Safety

A specific corrected QT interval study could not be conducted since very low plasma levels seen after oral fidaxomicin dosing in healthy subjects makes such a study not feasible. In phase 3 trials no clinically relevant differences between the fidaxomicin and vancomycin groups were noted with respect to changes in QTcB or QTcF intervals or other ECG parameters.

Use in Pregnancy and Lactation

No adequate and well-controlled studies with fidaxomicin have been conducted in pregnant women. A case of pregnancy in the fidaxomicin group has been discussed in the serious adverse event section of the briefing document.

VII. ISSUES FOR DISCUSSION

1. Has the applicant demonstrated the safety and effectiveness of fidaxomicin for the requested indication, treatment of *Clostridium difficile*-associated diarrhea (CDAD)?
   - If yes, are there any specific issues that should be addressed in labeling?
   - If no, what additional data are needed?

2. Is the finding of lower recurrence of CDAD at Day 31 in the fidaxomicin-treated subjects of clinical significance?
   - If yes, does it warrant discussion in product labeling?
   - If no, what additional data are needed?

APPENDIX A: JUSTIFICATION FOR A NONINFERIORITY MARGIN FOR THE ACTIVE COMPARATOR VANCOMYCIN IN TREATMENT OF CDAD

The pre-planned noninferiority margin of 10% proposed by the Applicant for the active comparator of vancomycin[4] is justifiable. This section describes the FDA's rationale for accepting this margin. Both our and the Applicant's rationales use the results of vancomycin versus tolevamer[5] trial as the basis for deriving the treatment effect of vancomycin. The applicant's rationale uses only the published results from the review by Weiss 2009. Our comparison of the trials in this document is more extensive and it relies on publications by Louie et al 2006, Louie et al 2007, Bouza et al 2008, Weiss 2009 and summary of the trials in clinicaltrials.gov. In addition to the derivation of the treatment effect, our comparison includes a discussion of similarities and differences between the historical trials and current trials as well as a discussion of evidence from vancomycin placebo trials.

First, we describe the available historical evidence to estimate the treatment effect of vancomycin against placebo and the reasons for choosing the two trials of vancomycin compared to tolevamer to derive the margin. Then, the plausibility of the constancy assumption is discussed by comparing the historical trials to the current trials with respect to the patient characteristics, endpoints and main inclusion criteria. Finally, we discuss the process of derivation of the non-inferiority margin.

Historical Evidence of Sensitivity to Vancomycin in Treatment of CDAD

Placebo-controlled studies provide the most direct estimate of an active comparator's drug treatment effect. However, there is limited information on effect of vancomycin compared to placebo for treatment of CDAD. The Cochrane review (Nelson 2007) identified only two randomized studies comparing vancomycin to placebo for treatment of C. *difficile* infection: Keighley 1978 and Johnson 1992. Johnson's 1992 study is not appropriate for our NI derivation because while the patient population in that trial was stool positive for *C. difficile,* they did not have diarrhea and diarrhea is an important symptom of CDAD. Keighley's 1978 study was originally used to derive the noninferiority margin because it was the more relevant vancomycin-placebo trial available when current trial 003 was planned. A discussion of characteristics and results of this study are shown in the next two sections.

More recently, results of two large randomized, double blind, and controlled studies demonstrating the superiority of vancomycin to tolevamer have been published (Louie et al 2007, Bouza et al 2008 and Weiss 2009). We use the results of these two later trials,

[4] That is oral vancomycin 125mg, 4 times a day, for 10 days.
[5] That is tolevamer 3g, three times a day, for 14 days

referred to 301 and 302 for the purposes of this appendix, to estimate vancomycin's treatment effect while considering tolevamer as putative placebo. It is assumed that the efficacy of tolevamer is no worse than placebo. However, as the poster by Louie et al. (2007) indicates for trial 301, tolevamer's efficacy may not be much better than placebo since 48% of subjects in the tolevamer arm did not complete treatment and the main reason for dropping out of the study was non-response to treatment (28% of subjects in tolevamer arm). Details of the design of trials 301 and 302 and how they compare to the current trials is provided in the next section.

Comparison of Historical Trials to Current Trial

Comparison of historical studies to current trials is important to establish the validity of the constancy assumption. That is, there is reliable data that vancomycin's effect would not differ between studies conducted today and the historical studies.

There is little support for the constancy assumption between the Keighley 1978 trial and the current CDAD trials. First, susceptible populations to CDAD and C. *difficile* strains have changed over time (see Aslam et al 2005), so results from Keighley 1978, a > 30 year old study, may not apply to the current CDAD population. Moreover, Keighley's 1978 design varied substantially from current CDAD trials with the most important difference being the duration of treatment of vancomycin (4 times a day for 5 days compared to 4 times a day for 10 days in current trials.) Additionally, there are several major quality concerns with this study including inadequate follow-up, and mislaid or missing specimens. When the poor quality of the trial and the small size are taken into consideration, the study results should be used with caution.

The constancy assumption between trials 301, 302 and current trials is plausible as trials 301 and 302 have similar design characteristics, inclusion criteria, and clinical trial populations compared to the two current studies under review. We describe in the remainder of this section the similarities and differences between trials 301, 302 and current trials 003 and 004. Design characteristics are summarized in Table 11, clinical trial subjects' characteristics are summarized in Table 12, and main inclusion criteria are shown in at the end of the Appendix.

Similarities in the design characteristics include the following (see Table 11): first, all studies are randomized, double blind, parallel arm with an active control comparator of vancomycin 125 mg every 6 hours for 10 days; second, studies 301 and 302 are contemporaneous to the current trials 003 and 004 with similar geographic distributions of multinational sites. Thus, the strains of C. *difficile* and susceptible populations are likely to be similar. Most of the sites in the historical studies and the current studies are in the United States and Canada, with some sites in Europe. Finally, the key inclusion criteria and definition of CDAD are similar although not identical.

One subtle difference in study design between trials 301, 302 and current trials 003 and 004 is the difference in definition of clinical cure and its assessment. In study 301 (Louie

et al 2007), clinical cure was defined as resolution and the absence of severe abdominal discomfort due to CDAD for two contiguous days including Day 10. Resolution was not defined in detail for the Phase 3 trial in Louie et al 2007, however it is defined in detail for the Phase 2 trial in Louie et al 2006. In Louie et al 2006, resolution is defined as 2 consecutive days on which the patient had any number of stools with an average consistency classified as hard or formed, or ≤ 2 stools with an average consistency of loose or watery. In addition, stool counts and average consistency were patient reported outcomes recorded daily (on days 1–14) by the clinical trial's nurse and/or investigator team after direct assessment and interview of hospitalized patients, and by daily telephone interview of outpatients on nonclinic days. In the current trial, clinical cure is a clinician reported outcome relying on whether continuation of CDAD therapy is indicated based on resolution of diarrhea. More precisely, under the cure checkbox, clinicians could see the following definition for cure:

- Subjects who, in the opinion of the Investigator, require no further CDAD therapy 2 days after completion of study medication will be considered cured.
- Subjects who have 3 or fewer unformed stools for 2 consecutive days and remain well prior to the time of study medication discontinuation will be considered cured. Alternatively, subjects who at the end of treatment have had a marked reduction in the number of unformed stools but who have residual and mild abdominal discomfort interpreted as recovering bowel by the Investigator may be considered cured at that time, providing no new anti-infective CDAD therapy is required.
- Subjects who are considered cured based on stabilization and improvement in CDAD signs and symptoms will be evaluated 2-3 days after study medication. In the event that their signs or symptoms of CDAD worsen, they will be designated primary failures. If they remain stable and are not considered to require further CDAD therapy to maintain their stable state, they will be followed for recurrence as cures.
- Subjects having a rectal collection device who are passing liquid stools periodically during the day will be considered to have resolution of diarrhea when the volume (over a 24-hour period) is decreased by 75% compared to admission or the subject is no longer passing liquid stools.
- Subjects who enter the study without signs or symptoms of CDAD, other than diarrhea will be evaluated as failures on the basis of continued diarrhea alone as defined in thee protocol.

A review of the baseline characteristics of population in studies 301, 302 compared to the population in current trials 003 and 004 (see Table 12) shows a largely similar clinical trial population in terms of age, baseline severity of the disease determined by number of stools, white blood count, and CDAD history (first episode or a re-infection).

Table 11: Main Design Characteristics of two historical trials and the two current trials

Trials	**Tolevamer Studies**	**Current Studies**
General	Randomized, double blind, parallel arms	
Multinational sites	Study 301: 91 sites in US and Canada (Louie et al 2007 and clinicaltrial.gov)	Study 003: 75 sites in United States, 23 sites in Canada
	Study 302: sites in Australia, Canada, and Europe. Total of 135 sites listed in clinicaltrial.gov.	Study 004: 30 sites enrolled subjects in the US, 11 sites enrolled subjects in Canada, and 45 sites enrolled subjects in Europe.
Treatment arms Randomization Total number of subjects	1- Vancomycin 2- Tolevamer 3- Metronidazole 1:2:1 randomization scheme Total number of subjects in ITT: 1420	1- Vancomycin 2- Fidaxomicin 1:1 randomization scheme Total number of subjects in mITT: 1105
Start date-end date	301: March 2005 to February 2007	003:09 May 2006 to 21 August 2008
	302: May 2005 to August 2007	004: 19 April 2007- 11 December 2009
Duration of treatment	10 days	10 days
Number of visits	Daily Assessments	Daily Assessments
Assessment of cure	Day 10	EOT to day 12

Table 12: Clinical Trial Subject Characteristics

Trials	Tolevamer Studies Pooled 301 and 302	Current Studies Pooled 003 and 004
Age (years) Mean (SD) Min, Max	 64 (17)[1] Not available	 62 (17) 18-94
CDAD severity[2] Mild Moderate Severe	 Mild (31%), Moderate (43%) Severe (25%)	 Mild (28%) Moderate (34%) Severe (37%)
CDAD history First occurrence	 First occurrence (83%)	 First occurrence (84%)

Recurrent	Recurrent (17%)	Recurrent (16%)

1. Age mean and standard deviation for the 301 trial (see poster by Louie et al 2007) , no data on age was available from publications for trial 302.
2. In tolevamer studies, the definitions are the following (see poster by Louie et al 2007) (1) Mild: 3-5 bowel movements per day, WBC less or equal to 1500 mm^3 and no abdominal pain (2) Moderate: 6-9 bowel movements per day, WBC 1501-2000 mm^3 and no, mild or moderate abdominal pain (3) Severe: 10 or more bowel movements per day, WBC greater or equal to 20001 mm^3 and severe abdominal pain. In current studies, the definitions are the following (1) Mild: 4-5 unformed bowel movements per day and WBC less or equal to 12000 mm^3 (2) Moderate: 6-9 unformed bowel movements per day and WBC between 1201-1500 mm^3 (3) Severe: 10 or more unformed bowel movements per day and WBC greater than 1500 mm^3

Determination of the Non-Inferiority Margin for Vancomycin in the treatment of CDAD

The results for clinical cure on the intent to treat population for studies 301 and 302 are shown in Table 13. A meta analysis of the results using the DerSimonian and Laird approach (random effect model) gives an estimate of the treatment effect of 37% with **95% CI of (30%, 43%).**

Table 13: Summary of Clinical Success Rate of Historical Trials (from Louie et al (2007) and Bouza et al (2008)): Intent-to-Treat Analysis

Study	Agent	Clinical Cure rate		Treatment Difference (95% CI)[2]
301	Tolevamer	124/266	46.44%	
	Vancomycin	109/134	80.74%	35% (25% -43%)
302	Tolevamer	112/268	41.64%	
	Vancomycin	101/125	80.16%	39% (29%- 47%)

1. Intent to Treat Set: includes all randomly assigned patients who received at least 1 dose of study drug, with any post dosing Investigator Evaluation data.
2. Confidence interval was derived using method recommended in Newcombe 1998 and Agresti and Caffo (2000).

Keighley's 1978 study shows that 9 out of 12 subjects in the vancomycin group had a resolution of diarrhea compared to 1 out of 9 subjects in the placebo group which gives a 95% confidence interval for the difference in proportion of (21% - 82%)[6]. However, as explained in the previous section, the results of this trial should be considered with caution as the constancy assumption does not hold, trial conduct was poor, and sample sizes are small.

[6] Confidence interval was derived using the method recommended in Newcombe 1998 and Agresti and Caffo (2000).

In summary, the overall data supporting a reliable and reproducible treatment effect was estimated only from the two studies outlined in Table 3. On one hand, this estimate may be conservative as tolevamer may have higher antimicrobial activity than placebo. On the other hand, there are uncertainties in the consequences of departing from the constancy assumption for vancomycin treatment effect and uncertainties in the generalizability of the results. These departures from the constancy assumption and generalizability issues include the following:

1. Potential difference in prognostic factors and inclusion/exclusion criteria
2. Differences in the definition of clinical cure compared to that used in current trials
3. Differences in disease severity at baseline
4. Limited historical data
5. Inter-trial variability of the estimate of active control treatment effect

To account for these uncertainties, the treatment effect estimate from the meta-analysis is discounted to estimate M1. We propose a discounting of 10%-15% and an M1 in the range of 26%-27%. This amount of discounting is based on our evaluation of the potential effect of the sources of uncertainties 1-5 above on the estimated treatment effect of vancomycin. In our derivation, the 10-15% discounting is applied to 30%, the lower limit of the 95% CI of the treatment effect of vancomycin over tolevamer from meta-analysis above. We acknowledge that the true treatment effect of vancomycin over placebo is probably larger than the estimate from the meta-analysis considering that tolevamer may have some antimicrobial activity.

In conclusion, the historical evidence supports the Applicant's proposed margin of 10% while still preserving over 60% of the treatment effect based on clinical judgment.

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Historical trials key inclusion criteria (from Poster by Louie et al 2007)

• Patients with non-life threatening medical conditions and an acute episode of documented (primary or recurrent) or presumed (recurrent) *Clostridium difficile* associated diarrhea (CDAD).
• ≥ 18 years of age
• The presence of CDAD at the time of enrollment with no other likely etiology for the diarrhea. CDAD was defined as ≥ 3 bowel movements in a 24 hour period (BM/day) with an average consistency of loose or watery, with a positive *C. difficile* toxin assay (EIA or cellular cytotoxicity assay) or pseudomembranes on endoscopy, and no other likely etiology for the diarrhea.
• ≤ 48 hours of treatment with metronidazole, vancomycin or other antibacterial therapy specific for CDAD within the 5 days prior to enrollment
• Baseline serum potassium ≥ 3.0 mmol (meq)/L
• Patient considered clinically stable to complete the 6 week study period
• No contraindication to oral / enteral therapy
• Absence of fulminant *C. difficile* disease

Current trials inclusion/exclusion criteria:

Inclusions

1. Male or female inpatients or outpatients, who were 16 years of age or older and who had CDI as defined by:
− Diarrhea: defined as a change in bowel habits, with >3 unformed bowel movements (UBMs; or >200 mL unformed stool for subjects having rectal collection devices) in the 24 hours before randomization, and
− Presence of either toxin A or B of C. difficile in the stool within 48 hours of randomization.
2. Female subjects of childbearing potential were required to have been using an adequate and reliable method of contraception (e.g., barrier with additional spermicide foam or jelly, intrauterine device, hormonal contraception); females who were postmenopausal must have been postmenopausal ≥1 year. Subjects (both male and female) must have agreed to avoid conception during treatment and for 4 weeks following the end of study treatment.
3. All subjects were required to sign an informed consent form.
4. Opiates were permitted as long as the subject was on a stable dose at the time of randomization and was expected to maintain this dose during the treatment period.
− as needed opiate was permitted as long as the total daily dose was not changed during the treatment period.
5. Individuals who failed at least a full 3-day course of metronidazole but continued to meet the definition of diarrhea without any significant clinical improvement and remained toxin positive could be enrolled in the study.

Exclusion

1. Life threatening or fulminant CDI (white blood cell [WBC] count >30 × 109/L; temperature >40°C; or evidence of hypotension [systolic blood pressure less than 90 mmHg], and septic shock, peritoneal signs, or significant dehydration).
2. Toxic megacolon.
3. Previous exposure to fidaxomicin
4. Females who were pregnant or breastfeeding.
5. Likelihood of death within 72 hours from any cause.
6. Concurrent use of: oral vancomycin, metronidazole, oral bacitracin, fusidic acid, rifaximin, nitazoxanide, or related drugs. If the Investigator felt a clinical imperative to begin treatment before knowing the laboratory result for stool toxin, up to 4 doses but no more than 24 hours of treatment with metronidazole and/or vancomycin were allowed. While such pretreated subjects could be enrolled (i.e., no more than 24 hours of previous therapy), it was preferred that subjects be enrolled who had not received prior CDI treatment on this admission. The Investigators were encouraged to identify eligible subjects, whenever possible, before other therapy was given and to "sensitize" their institution to this study so that subjects could be entered without prior therapy.
7. The anticipated need to continue other antibacterials for a period exceeding 7 days from study start.
8. Subjects who, in the opinion of the investigator, required other drugs to control diarrhea (e.g. loperamide) or that could affect peristalsis.
9. Unable or unwilling to comply with the study protocol, including ingesting capsules, having blood drawn, and providing stool samples as scheduled.
10. Participation in other clinical research studies utilizing an investigational agent within 1 month before screening or within 5 half-lives of the investigational agent, whichever was longer.
11. History of ulcerative colitis or Crohn's disease.
12. Multiple occurrences (defined as more than 1 prior occurrence) of CDI within the past 3 months; subjects presenting with the first recurrence within 3 months could be enrolled.
13. Subjects whom the investigator felt were inappropriate for the trial, e.g. subjects with known hypersensitivity to vancomycin.